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(PRIMARY) AGRANULOCYTIC ANGINA

by

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PRIMARY AGRANULOCYTIC ANGINA

INTRODUCTION

Since its original description by Schultz (1) in 1922, agranulocytic angina has come to occupy more and more prominence in the medical field. Today the literature is flooded with a heterogeneous array of case reports, many theories of etiology, clinical and laboratory manifestations, and biopsy and necropsy findings. Added to this is a confusing terminology, various attempts at classification, diverse forms of treatment, and many arguments both pro and con as to whether or not agranulocytic angina is a disease entity, a group of diseases, or only a symptom complex.

Very little critical reading is necessary before one is aware that the term "agranulocytic angina" is now being used as loosely as was formerly the term "anemia", that is, any clinical manifestation of a neutropenic state irrespective of the cause or the clinical or laboratory picture is being reported more or less constantly as a case of agranulocytic angina. It is little wonder that the ultimate summation of the present day literature to the average reader is very contradictory and to him the subject as a whole is surrounded by a maze of assertions and denials, conflicting ideas, confusing terminology and great diversity of treatment. Excellent proof for this is seen in so many cases: the acute onset was dramatic from

480484

INTRODUCTION

the first and yet the case was sadly mismanaged as a tonsillitis or a common influenzal attack until complications made the outcome inevitable. The element of time is a most important factor and the prognosis at best is extremely grave. It is worth noting that the isolated cases reported in the literature carry a heavier mortality than those reported in series as patients of a single individual or group. This difference in mortality is probably not due to the better ability of the latter to prescribe a certain type of therapy, but to the ability to make an early diagnosis and institute supportive as well as prophylactic treatment and exercise complete control over the patient before the case is hopelessly beyond control.

The last word in this clinical syndrome most certainly has not been written, but much can be found that is of genuine value. In this presentation an attempt will be made to offer a clear understanding of the present day subject as a whole, with particular reference to special considerations of etiology, pathogenesis, diagnosis and rationale of treatment.

DEFINITION

The definition of primary agranulocytic angina that follows has been adapted with slight modifications from that recently offered by Beck (2):

Primary agranulocytic angina is a grave disease of unknown etiology, characterized by a marked reduction in the total number of white cells and a complete or near complete absence of granulocytes in the peripheral blood stream, accompanied by aplastic, normal or hyperplastic myeloid tissue. Following the peripheral neutropenia there may be any number of lesions and symptoms which might follow the removal from the body of such an important defense mechanism. The disease may be acute, recurrent or chronic.

Note: Hereafter, in instances in which the designation "agranulocytic angina" is used without further qualification, primary agranulocytic angina is to be understood.

HISTORY

Agranulocytic angina is a disease of apparent recent origin. As has been pointed out by Beck (2), had it existed to any great extent prior to 1922, it undoubtedly would have been described long before, since the disease runs such a dramatic course and usually terminates fatally. Too, blood counts have been a routine procedure in most large hospitals for the past fifty years. Pepper (3) in his history of agranulocytic angina recently pointed out that "putrid sore throat" and "gangrenous angina" probably represent the same condition as seen and described by the laryngologists of the last century. In his manual of diseases of the throat and nose, Mackenzie (4) credited Gubler, in 1857, and Trousseau, in 1865, with having definitely differentiated the disease from diphtheria. The first case to be cited in America was probably that of Brown (5), who in 1902 reported a fatal case of acute primary infectious pharyngitis with extreme leukopenia. Schwarz (6) in 1904 and Turk (7) in 1907 published case reports similar to that of Brown. Leale (8) in 1910, reported a case in a male child two and one-half months old under the title of "Recurrent Furunculosis in an Infant Showing an Unusual Blood Picture". Baldrige and Needles (9) have found a case of undoubted agranulocytic angina in the 1910 records of the University

HISTORY

of Iowa Hospital, pointing out that in former years it either was overlooked because the blood was not examined or was interpreted as a symptom of exhaustion of the bone marrow, aleukemic leukemia or aplastic anemia.

However, it was not until 1922 that Werner Schultz(1), recognizing this rapidly fatal symptom complex, designated it "agranulocytosis" and stated the belief that this symptom complex was a distinct clinical entity. The essential clinical features of a typical case of agranulocytic angina as set forth by him were: sudden onset in the midst of good health; a leukopenia with absence or near absence of granulocytes in the blood stream but with a relative conservation of the red corpuscles and the erythropoietic tissue; a progressive gangrenous process, usually in the throat; a prostrating fever; and an acute clinical course with a fatal termination.

With but few additions, this picture of agranulocytic angina still stands. Although denied by many, there are probably just as many who accept this clinical syndrome as constituting a new disease entity in the sense that pernicious anemia is a disease entity, although the final word in both instances in this regard can not be said until the etiology of both is known.

With the original description of Schultz, a new impetus was given to the restudy and analysis of those leukopenic states primarily reflecting a relative and absolute decrease

HISTORY

in granular leukocytes. Cases have been recognized in practically all parts of the world and the literature devoted to the subject has become voluminous. In the five year period subsequent to 1922, Kastlin (10) was able to find but forty-three cases in the literature, but in the six years following Kastlin's report, the incidence has increased rapidly and, according to Madison and Squier (11) there are now more than five-hundred cases on record.

NOMENCLATURE

The nomenclature associated with the syndrome best known as agranulocytic angina is very confusing and is often misleading. The original names, that of agranulocytosis, first proposed by schultz (1) in 1922, and angina agranulocytica, suggested by Friedemann (12) the following year, were very unfortunate choices, particularly when the supply of hematologic terms is so abundant that there is little excuse for choosing such ambiguous ones. As has been pointed out by Schilling (13), the name agranulocyte was originally chosen for "neutrophils without granulations" seen in blood smears from cases of leukemia. Agranulocytosis therefore means an increase in these atypical neutrophils and suggests a leukemic syndrome which of course is not intended. Angina is likewise unfortunate because of its essential ambiguity, that is it implies that one is dealing with an infection in the mouth which causes neutropenia. Instead, the infections encountered are secondary to the neutropenia, the infection may or may not be located in the mouth, and cases have occurred where visible infection was entirely absent. Too, angina suggests a known etiology while in reality the etiology is utterly unknown.

Attempts to correct these early misnomers have resulted in a great many articles criticizing the names offered and suggesting other names more truly descriptive of the syndrome. The result of this vast array of names, some good,

NOMENCLATURE

some equally as unfit as the originals, has for the most part but served to increase the general confusion. More recently, many writers make no differentiation in names regarding the extreme neutropenic state whether idiopathic in nature, due to sepsis, chemical poisoning, irradiation, or to true aplasia of the red bone marrow. The terms granulopenia, granulocytopenia, mucositis necroticans agranulocytica, monocytic angina, hypo-granulocytosis, malignant sore throat, sepsis with granulopenia, monocytic angina, hypo-granulocytosis, and agranulemia are mentioned because of their not infrequent appearance in the literature and because they serve as examples of the present confusing terminology. Some of the better names that have been suggested are: idiopathic neutropenia, by Baldrige and Needles (9); malignant neutropenia, by Schilling (13); malignant (fatal) and benign (recovered) neutropenia, by Rosenthal (14); and pernicious leukopenia, by Fitz-Hugh and Krumbhaar (15). Mentally reviewing the definition of primary agranulocytic angina, it is seen that idiopathic neutropenia and pernicious leukopenia are probably the most descriptive and most accurate. Malignant neutropenia in itself is very good but in the literature, some authors term a severe neutropenic syndrome due to a known etiological factor as being malignant neutropenia (notably in England and to some extent in America), while others reserve the

NOMENCLATURE

name solely for the idiopathic syndrome. Some, may it be said, use the term interchangeably.

As a result, the name agranulocytic angina, although obviously at fault and even misleading, has been retained for the true designation of the syndrome in this presentation for the following reasons: it is the most generally accepted and most generally used term, it conforms to the Cumulative Index Medicus, and in all is less apt to lead to further confusion.

MYELOID TISSUE

Sound principles of treatment are invariably based upon an understanding of normal physiology and an appreciation of the abnormal physiology involved. It is now quite generally agreed that the question of agranulocytic angina has its answer in the myeloid tissue of the red bone marrow so that before proceeding to a discussion of the possible etiological factors in agranulocytic angina, or of the pathology found, or of a rational treatment, it becomes necessary to consider first the physiology of the myeloid tissue together with its components.

In the normal adult the myeloid blood elements, the red blood cells and the granulocytes, are produced exclusively in the red bone marrow and probably the platelets as well. The bone marrow is composed chiefly of two kinds, the red bone marrow and the yellow bone marrow. The latter resembles subcutaneous adipose tissue and does not contribute to the production of blood cells but, according to both Maximow (16) and Sabin (17) it does have potentialities to become converted into, or give place to the red bone marrow in times of abnormal conditions such as after considerable hemorrhage or in the anemias. The remarkable lability of the yellow bone marrow has been demonstrated by Doan (18) who showed that the fat can be demobilized from the bone of a bird in 48 hours. He also found that when the fat disappears so rapidly from the marrow, its place is not at once completely occupied by blood forming tissue, which has no such speed of regeneration,

MYELOID TISSUE

but its place is rather rapidly occupied by a gelatinous substance which fills in all the spaces left by the shrunken fat cells. It is in this gelatinous marrow that new myeloid tissue develops. As Sabin (17) has pointed out, pathologists have long regarded gelatinous marrow as being a stage or form of degeneration but from many observers it becomes evident that hematopoiesis begins in the gelatinous marrow after hypoplasia. These points should be kept well in mind during the discussion of the pathology found in the bone marrow in cases dying with agranulocytic angina.

During fetal life and in the newborn, the cavities of all bones contain only the red marrow. Soon after birth there is a gradual replacement of the red bone marrow by yellow bone marrow so that in the adult, the red bone marrow is found only in the vertebrae, the ribs, sternum, the diploe of the bones of the skull, os innominatum, the proximal end of the epiphyses of the femur and humerus, and in a thin sheet at the periphery of the yellow bone marrow in the diaphyses of these bones. (16).

Taken collectively the red bone marrow or myeloid tissue forms an organ of considerable size and, according to Beck (2), has been shown by Wetzel in the adult to be but slightly smaller than the liver. Doan (19) has called attention to the fact that the hemopoietic organ has all the potentialities for hypertrophy and atrophy and functional insufficiency that appertain to any other organ or tissue of the body. Normally

MYELOID TISSUE

this organ is quite uniform throughout, that is, the ratio of erythropoietic to granulopoietic tissue is quite constant and the various levels of proliferation and maturation are everywhere alike. This has been demonstrated by Doan and Zerfas (20) and, although they found no definite ratio of erythropoietic to granulopoietic tissue between normal individuals, they did find a uniformity in ratio for the individual. These ratios were estimated to be from 1:5.5 to 1:20, demonstrating the larger size of the granulopoietic organ and indirectly supplying evidence that the life of the granulocytic cell is very short lived and a fragile production considering the size of the respective organs and the relative number of the separate cell types in the peripheral blood stream.

The histological considerations of the myeloid tissue that follow have been taken from the work of Maximow (16):

In the myeloid tissue, two structures have to be distinguished : (1.) the supporting spongelike framework or stroma which is intimately connected with the blood vessels; and (2.) the free elements in the meshes of the stroma. In the former the blood vessels demand further consideration and it is in the latter that we are particularly interested in this work because in the free elements in the meshes of the stroma are found the precursors as well as the mature myeloid elements before they are delivered to the blood stream.

The circulation within the bone marrow is accomplished

MYELOID TISSUE

chiefly by the main nutrient artery and its accompanying veins, which pass toward either epiphysis. The arterial and venous systems are separated by a capillary network peculiar to itself in that in this network are found large and very numerous venous sinusoids. These sinusoids constitute the functioning vascular bed of the myeloid tissue and maintain constantly a maximum supply of blood. Their walls are formed not by common endothelium, but by a very thin syncytial membrane composed of greatly flattened histiocytes or littoral cells.

The free elements in the myeloid tissue are the mature myeloid elements, a few cells which in every respect are identical to small lymphocytes, and the immature myeloid elements. The mature elements are the non-nucleated red blood cells, the three types of granular cells, and the megakaryocytes. The two former types are indistinguishable from those in the blood stream and only await the factor which will call them into the circulation. In this study the small lymphocytes and the megakaryocytes are without apparent importance. Of the immature myeloid elements, the ones with which we are concerned are the erythrocytic and granulocytic young forms.

Pathological findings apparently are not in evidence in the precursors of the parent cell of the myeloid elements. It is not necessary therefore to consider here the several differences of opinion upon this subject. But, starting with

MYELOID TISSUE

the parent cell of the myeloid tissue, the hemocytoblast of Maximow (myeloblast), most hemotologists agree to the following: The hemocytoblasts proliferate by mitotic division and during this division a peculiar unstable equilibrium of the cell develops at the height of the mitotic process. It is at this time that one of the various latent potencies manifests itself: one is followed and both daughter cells which originate from such a mitosis at once show new properties. If the balance turns one way, the daughter cells are proerythroblasts; if it swings the other way, a pair of promyelocytes of one of the three forms is determined. The proerythroblasts and promyelocytes are specific differentiated elements. Each is capable not only of proliferation but also of further development into mature erythrocytes and granulocytes. Normally only a part of the young forms reach maturity, the others remain unused in the tissue. This source of myeloid blood elements from elements of the same type is termed homoplastic hemopoiesis and is the usual source of erythrocytes and the granulocytes. Under pathological conditions, where an unusual demand is made upon the myeloid tissue, not only do mitoses of pre-existing proerythroblasts and promyelocytes continue, but in addition, new cell strains of the type needed are formed from the hemocytoblasts as already described and is termed heteroplastic hemopoiesis.

A study of the intermediary stages of development between

MYELOID TISSUE

the proerythroblast and the mature non-nucleated red cell is not necessary here. Many intermediary cell types are described in the development of the granulocytes but for this study only the following need be considered: Starting with the promyelocyte, in sequence of development we find, the promyelocyte, myelocyte, metamyelocyte, staff cell, and the mature granulocyte. The first two forms proliferate by mitotic division but beginning with the metamyelocytes, the capacity for division is lost. Other important factors to be kept in mind when pathological studies of the myeloid tissues are discussed are: (a.) Within the red bone marrow is found all ages and stages of development of the granulocyte from the hemocytoblast to the segmented granulocyte. (b.) In the peripheral circulation are found the segmented granulocytes, the staff cells, and a very small percent of metamyelocytes (juvenile form of Schilling, 1% being considered normal by him). (c.) Ameboid movement usually begins with the metamyelocyte and continues until the non-motile senile state is reached. This last state is found in the peripheral blood stream. (d.) Characteristic granules appear in the promyelocyte, reach maximum development in the myelocyte, and are a constant feature from this stage on. (e.) When there is an unusual demand for erythrocytes or granulocytes in the peripheral blood stream, it is not unusual to find the demand exceeding the supply of mature elements so that in

MYELOID TISSUE

the attempted physiological compensation, young forms appear in the circulation.

The mode of entrance of the myeloid tissue elements into the general circulation is much debated but according to Maximow (16) both the erythrocytes and the granulocytes develop extravascularly around the venous sinusoids, the older forms being found closest to the sinusoids. They both enter directly through the modified endothelium of these blood spaces. This wall is extremely thin and through it pass not only the ameboid cells but the non-motile erythrocytes as well. Maximow advances the theory that this phenomenon is probably regulated by changes in the permeability of the walls of the venous sinusoids and in the surface energy but offers no explanation for such changes. In agranulocytic angina the mode of entrance of the myeloid products is probably unimportant in comparison to the stimulus which is responsible for the initiation of this movement so that further consideration of the former point is unnecessary.

The factor or factors which bring about this emmigration into the blood stream is a question of much speculation. In the normal physiology of the hemopoietic organ there are two main functions to be considered; first, the growth of the cells, and second, their delivery to the circulation. The consensus of opinion is that the factors involved in these processes are a maturation factor to keep the growth

MYELOID TISSUE

development normal, and a chemotatic factor to call these cells to the blood stream. Vasomotor influences have never been definitely demonstrated. Instead, experimental investigation would seem to point toward a hormonal control.

Concerning the maturation factor governing the granulocytes, very little is known; but with respect to the erythrocytes, the work of Minot and Murphy (21) would seem to show that such a factor does exist in liver, and a year later, 1927, Cohn and his associates (22) isolated from liver a specific substance rich in this maturative agent. Subsequent workers too numerous to mention have made similar extracts from other organs, notably the stomach, kidney, and spleen. According to Beck (2), liver extracts so far have never been shown to supply a maturation factor for granulocytes. However, Goldhamer et al. (23) studying short interval observations on the blood in pernicious anemia patients after non-purified liver extract intravenously, report a temporary increase in the white blood cell count as do Riddle and Sturgis (24) under like circumstances, each group of men considering such findings as a bone marrow stimulation (maturation) phenomenon. Within the past year Miller and Rhoads (25) have shown that the intravenous injection of liver extract causes a marked rise in the white blood cell count but due to splenic contracture rather than to an effect upon the myeloid tissues. Considering the physiology of hemopoiesis, the well known rise of the

MYELOID TISSUE

leukocytes in the blood stream that eventually takes place following liver therapy in pernicious anemia seems far more likely to be due to a release of the hemopoietic function from excessive erythrocytic production rather than to a direct effect upon the granulopoietic tissue.

Doubtless a similar maturation factor does exist for granulocytes as has been shown apparently exists for erythrocytes but as yet no definite agent has been demonstrated. The most probable sources in the light of our present day knowledge are glandular extracts, dietary research, vitamins, and biological chemistry.

With respect to the chemotatic factor, much more is known than that relative to the maturation factor. Today, many agents are known to cause an increase in the percentage of polymorphonuclear neutrophils in the peripheral circulation, such as muscular exercise, cold baths, change from recumbent to the upright position, pilocarpine, atropine, toxemic conditions, foreign proteins, certain bacteria, mechanical stimulation to the vaso-motor nerves, nucleic acid and its decomposition products guanine and adenine.

The phagocytic power of the polymorphonuclear neutrophil was first emphasized as far back as 1892 by Metchnikoff. For a short time this initiated an era of intensive cytological investigation and during this period a considerable amount of study was devoted to means or methods by which body defenses (immunity) might be increased. This work was soon overshadowed

MYELOID TISSUE

by the rapidly growing interest in humeral immunity. However brief this intensive study of the polymorphonuclear neutrophil was, of interest today was the use at that time of nucleic acid on purely empirical ground to supposedly increase the germicidal power of the blood.

Shortly following the original description by Schultz of a syndrome whose most striking characteristic was an idiopathic neutropenia, a new impetus was given to the re-study and analysis of those leukopenic states primarily reflecting a relative and absolute decrease in neutrophilic leukocytes. Outstanding in this field of research are Doan and his co-workers and from them have come not only many detailed studies on the physiology of the polymorphonuclear neutrophil under both normal and pathological conditions, but also numerous controlled observations demonstrating the existence of a chemotactic factor for granulocytes and even the possibilities of a maturation factor as well. They have shown that the bone marrow delivers its cellular products in response to an ever-varying functional demand, both the physiologic (26) and the pathologic (20) ranges in cell levels obeying definite laws of rhythmic equilibrium. In the normal individual the rhythm of the white cells from hour to hour is in large part a reflection of variation in the polymorphonuclear neutrophils, because they are present proportionally in greatest numbers (26). Sabin (26) observed a similar rhythm of certain non-motile polymorphonuclear neutrophils (senile forms) in the

MYELOID TISSUE

peripheral circulation. With this observation in mind, Doan (20) suggested the hypothesis that the normal stimulus for maintaining the equilibrium of the polymorphonuclear neutrophil might be liberated products from disintegrating cells of the same type, that is from these senile forms. This could occur either directly or through the medium of the phagocytic group of cells reducing the debris. To further substantiate this hypothesis, he was able to show a correlation between the "showers" of non-motile forms in human pathologic conditions and the subsequent increase of young motile neutrophils. At the same time, Jackson (27) was demonstrating for the first time the existence in normal human blood of pentose nucleotides which he found to arise from the continuous physiologic degeneration of the granulocytes in the blood stream. Historically it is of interest to know that nucleic acid was isolated by Altmann in 1877 from nuclear debris constituting the pus so readily available from human patients in those days of septic surgery. Combined with Doan's former observations of the correlation between the showers of non-motile forms in human pathologic conditions and the subsequent increase of young motile neutrophils, the work of Jackson suggested a new avenue of approach, that is, the reaction of the myeloid tissue following the hypodermic injection of nucleic acid or its degradation products. Further consideration of these experiments and those of other workers in the same field will be discussed later under the

MYELOID TISSUE

rationale of treatment: at this point only a summary of Doan's (19) observations is necessary:

"Nucleic acid and its degradation products exert a chemotactic effect on normal myeloid foci with a prompt effective increase in the delivery of granular leukocytes to the peripheral circulation under a controlled physiologic or rhythmic mechanism.

"Repeated large intravenous injections tend neither to exhaust nor to cause a malignant hyperplasia of the myeloid elements in normal animals.

"A short course of injections stimulates a myeloid hyperplasia of normal marrow without otherwise injurious consequences, which is reflected by a relative and absolute increase in the amphophilic granulocytes in the blood stream of rabbits."

The functions of the granular leukocytes are but little known and are even less understood. In a summary of the functions of these cells, Clough (28) has stated that the neutrophil possesses amoeboid movements and has the ability to engulf bacteria and pigment granules, that is, they are phagocytes. He further states that these cells possess a variety of oxidative and proteolytic ferments in their cytoplasm, and as a result of such ferment activity, engulfed bacteria and other "digestible" objects undergo solution within the cell. This phagocytosis and intracellular destruction of bacteria is a manifestation of one of the important functions of these leukocytes; namely, the

MYELOID TISSUE

power to combat infection. This activity is manifested especially toward the pyogenic cocci. Other species of micro-organisms such as the tubercle bacillus may be little affected by them. However, Clough adds that there is little doubt but that these cells possess other functions that may be of equal importance but are not as well established by experimental evidence and are much less clearly understood--namely, they may be a source of the antitoxins and antibacterial substances of the plasma, and a source of some of the ferments of the blood. Finally, a great number of these leukocytes are lost to the body daily through the mucous membranes and they undoubtedly carry with them and remove from the tissues considerable quantities of undesirable particulate matter, and conceivably of substances in solution as well.

Concerning the basophils, nothing definite is known. Of the eosinophils, ameboid movement is present but less actively so than in the neutrophils. Clough states that phagocytosis is occasionally observed but is rare. Because their number is increased in certain diseases associated with protein hypersensitiveness and in infections with animal parasites, it may be inferred that they serve a specific function in bringing about the disintegration and removal of foreign protein from the tissues, and in combating animal parasites.

Nothing is known for the cause of a leukopenia in certain infections such as influenza, typhoid etc.

ETIOLOGY

It is generally admitted that the basic pathological manifestation in primary agranulocytic angina is found in the myeloid tissues but to date no etiological factor has been demonstrated to be the specific causative agent. Even the concept of agranulocytic angina as a disease entity rather than a mere hemotologic manifestation of various unrelated disorders is still open to question. Opinions of those who apparently have made a careful study of the subject are divided about equally as will be obvious in our considerations of pathological studies. Even so, whether a disease entity or only a symptom complex, an explanation of the pathogenesis of this syndrome rests on hypothesis alone. Various observers have implicated a great variety of possible causative factors and an attempt will be made to limit discussion of these according to their relative merits but it becomes evident that there is much overlapping and that in the last analysis the final word with reference to etiology has not been written.

Chemical Agents: Certain toxic substances, notably arsenic, benzene and products containing the benzene ring, have been known to produce a picture very similar to and in some cases indistinguishable from primary agranulocytic angina (2, 19, 29, 30, 31, 32, 33, & 34). Their importance is to be kept in mind because of the widespread use of arsenical preparations in the treatment of syphilis, the many uses of benzene in the industrial world, and the

ETIOLOGY

indiscriminate use of coal tar drugs (benzene derivatives) by the general public. Usually these products produce a toxic effect upon all the myeloid elements and not a selective toxicity for granulopoietic tissue alone as is shown by such various accompanying symptoms as those of purpura hemorrhagica and symptoms simulating aplastic anemia. Chemical intoxication will not account for the vast majority of cases described in the literature according to Beck (2), Roberts and Kracke (35), Dennis (34) and many others too numerous to mention, and even of more importance the syndrome produced by these substances fails to meet the requirements of primary agranulocytic angina by definition, that is, they constitute a known etiological factor. In fairness to those men who have described a syndrome like agranulocytic angina caused by chemical intoxication, let it be said that none of those quoted above consider extraneous chemical intoxication as being the etiological factor in all instances. However, most of them agree that chemical intoxication in certain instances may be a precipitating cause in susceptible individuals. Madison and Squier (11) have very recently reported in the J. A. M. A. (Mar. 10, '34) fourteen cases of agranulocytic angina in which a definite history was obtained in each case of the use of amidopyrine (in combination with a barbitol preparation, amidopyrine alone, or in one case in combination with other drugs) immediately prior to the clinical discovery of the disease. The administration

ETIOLOGY

of a single dose of amidopyrine to each of two patients who had recovered from the acute stage of the disease was followed by a rapid and profound fall in granulocytes. In summary they conclude that amidopyrine alone or in combination with a barbiturate is capable of producing primary agranulocytic angina in certain individuals who have developed sensitivity to the drug, and that the appearance of primary agranulocytic angina following the use of such drugs may be the result of an allergic or anaphylactoid drug reaction.

Micro-organisms: Because of the localized lesions found particularly in the oropharynx, gastro-intestinal tract, vagina, and skin; the not infrequent onset of symptoms immediately following teeth extraction or tonsillectomy; and the frequent finding of positive blood cultures during the acute stage--all these led numerous observers in the past as well as some at the present (1, 36, 37, 38 & 39) to consider that the disease was caused by a specific micro-organism. Two theories have been proposed: the first attributes the cause directly to a specific organism that precipitates the disease at the time the individual becomes inoculated; the second considers it to be caused by a hidden organism that remains dormant without any external manifestation whatsoever but produces an insidious selective intoxication of granulopoietic tissue so that any intercurrent infection in this individual acts the same as an overwhelming infection of extreme virulence in the average individual.

Experimental evidence has failed to substantiate the first hypothesis (36,37,38 & 40). That sepsis plays a

ETIOLOGY

major role is readily admitted but the concensus of opinion today believes infection to be a complication rather than a cause of agranulocytic angina. Certainly no conclusions as to any specificity can be made judging from the great variety of organisms so often isolated either from the blood stream or local lesions, such as, Vincent's spirillum, *B. fusiformis*, *B. coli*, *B. pyocyaneus*, *S. hemolyticus* and *viridans*, pneumococcus, and staphylococcus. Additional evidence against such a hypothesis may be briefly summarized as follows: the neutropenia may be periodic and definitely precede the appearance of local infection (2, 8, 19, 35 & 41); biopsy and post-mortem changes are revealing the fact that not in every case of peripheral leukopenia is the bone marrow aplastic for myeloid elements (15, 30 & 42).

With regard to the second hypothesis, Nakayama (43) and Gay and Oram (44) have shown that certain of the pyogenic bacteria are capable of producing a toxin which is specifically lethal for leukocytes, particularly granulocytes. This toxin they termed leukocidin. Following this lead, Dennis (34) introduced into the peritoneal cavity of rabbits leukocidin-producing organisms sealed in a collodion capsule. This capsule was permeable to the toxic products of the organisms but impermeable to the organisms themselves. He found that leukocidin-producing organisms, restrained from active invasion of the tissues but so situated that their diffusible toxic products could be absorbed, were capable of producing agranulocytic angina. Since merely the injection of filtrates

ETIOLOGY

of these same organisms consistently failed to induce a depression of the granulocytes, he concluded that the constancy of the supply of toxin is a highly important factor in the production of a detectable leukopenia. In conclusion he states that his conception of the usual origin of the clinical agranulocytic angina syndrome is that there is a primary focus of infection by one of the leukocidin-producing organisms from which leukocidin is diffused into the blood stream where it affects the neutrophils, and if present in sufficient quantity and toxicity, it injures the granulopoietic elements of the bone marrow. With the removal of the granulocytes and the cutting off of their supply, the body is liable to invasion and a fatal sepsis frequently results.

Allergy: This phenomenon is alluded to a number of times in the literature and a number of cases have apparently been precipitated in the human by anaphylactic reaction (45 & 46). Dameshek and Ingall (47) have expressed the opinion that agranulocytic angina is not a disease entity but is an abnormal reaction to sepsis or toxicity. Schilling (13) has given a similar opinion and was able to produce a blood picture very like that in agranulocytic angina by means of an experimental anaphylactic reaction. Delatour (48) attempts an explanation by stating that, since sepsis undoubtedly plays a role in this symptom complex, in the recurrent type it would seem that the bone marrow of some individuals

ETIOLOGY

is very sensitive and a reasonable explanation is that an overwhelming protein reaction on the bone marrow of a sensitive individual takes place, or that a sensitive granulocytic system is affected by the noxious agent of a septic process. The work of Madison and Squier (11) in which they describe a failure of the granulopoietic system due to drug sensitization has already been referred to under the heading of Chemical Agents as an etiological factor.

In contradistinction to some extent to the above observations and opinions, Fitz-Hugh and Comroe (49) reported that in their series of eighteen patients, in none of them could be found any convincing evidence of allergic disturbance.

Constitutional Predisposition: Roberts and Kracke (35) were among the first to recognize the importance of analyzing accumulated data in terms of white cell level and symptomatology. In a study of the records of 8,000 private clinic patients, one out of every four was found to have had a mild granulopenia; one out of every two women patients between the ages of 40 and 60 was neutropenic; and complaints of weakness, exhaustion and fatigue were twice as frequent in the granulopenic individuals as in those showing a normal white cell count. Furthermore, the severity of the symptoms to a remarkable extent were in direct proportion to the degree of granulopenia found.

In a very similar analysis of 10,000 case records of

ETIOLOGY

patients cared for in the University of California Hospital between 1920 and 1931 inclusive, Mettler and Olsan (50) found that examination of the blood counts revealed leukopenia in 1,167 or 11.7% of the cases and that 52.4% of the cases of leukopenia occurred in females and 47.6% in males. Leukopenia occurred frequently as a manifestation in patients with vague symptoms of one kind or another, chronic fatigue being the predominating symptom. The higher percentages obtained by Roberts and Kracke are probably due to their choice of 6,000 white blood cells per cubic millimeter of blood as the lower limit of normal while Mettler and Olsan took 5,000 leukocytes as the lower limit of normal. In view of such findings, Mettler and Olsan are ardent supporters of the concept of agranulocytic angina as suggested by Rosenthal (14) who said that in his belief, the chief etiological factor in agranulocytic angina is primarily a profound constitutional disturbance of the granulopoietic tissue. His conclusions are based upon a personal observation of 90 cases of marked leukopenia.

After consideration of the various types of pathology found in the bone marrow (it may be hypoplastic, normal, or hyperplastic for granulopoietic elements) Miloslavich (51) expressed a quite similar belief as Rosenthal. He attributes these variations in reaction to pathological functional expressions of individual character of a constitutionally weak, functionally readily insufficient and easily vulnerable

ETIOLOGY

bone marrow, depending also upon the type and virulence of the noxious agent. This constitutional (functional) inferiority of the bone marrow is vividly expressed in those instances in which an increased functional demand is urgently and vitally needed, but the bone marrow tissues respond with an alarming collapse and a rapid, complete exhaustion.

In opposition to the hypothesis of a constitutional predisposition are those who cite many known instances in which patients dying from agranulocytic angina have showed on previous blood examinations no tendency toward a neutropenic state and have on several occasions exhibited a normal leukocytosis in response to infection. Fitz-Hugh and Comroe (49) showed a number of such cases in their series of patients and concluded that these findings make it difficult to uphold the hypothesis of a constitutional predisposition to agranulocytic angina. However, it would seem that this conclusion is based upon inadequate consideration because too many instances are known in which other organs of the body function under a handicap for years, respond to added strain without gross manifestation, but decompensate if the load becomes too great. It is not at all unreasonable to think of a decompensation of a granulopoietic organ that is functionally inadequate to withstand too great a load.

ETIOLOGY

Congenital and Family Anomaly: In a discussion of the relations between acute aplastic anemia, acute aleukemic lymphadenosis and primary agranulocytic angina, Bickel (52) stated that in each of these blood dyscrasias, there is a strong possibility of a constitutional degenerative blood picture. Cases characterized by neutropenia and lymphocytosis will often show such a blood picture demonstrable in all of the patient's nearest relatives. He further asserted that such individuals react very promptly and intensely to certain noxae of the bone marrow. If these injurious agents injure suddenly and intensely the granulocyte-forming function, agranulocytic angina is found: if they gradually injure the blood-forming functions of the marrow, a picture of amyelia or aleukia develops which under certain circumstances may change into that of acute aleukemic lymphadenosis.

Apparently, similar studies to those of Bickel have not been made by American observers with the exception of Fitz-Hugh and Comroe (49). In none of their cases were they able to demonstrate even a suggestion of an hereditary or familial incidence of any blood dyscrasia. Pepper (41) states that in all his observations and reading, agranulocytic angina is apparently not familial.

A Manifestation of Other Blood Dyscrasias: There are occasional articles in the literature by those who consider agranulocytic angina to be an abnormal manifestation of other

ETIOLOGY

blood dyscrasias. This phase of the subject will be considered under Differential Diagnosis:

A Disturbance of Chemotactic and Maturation Factors:

The original exponents of this theory of etiology were Fitz-Hugh and Krumbhaar (15) and today the therapeutic agents that have shown the best results have been derivatives of nucleic acid which, according to the researches of Doan (19), are apparently maturative and chemotactic agents. Fitz-Hugh and Krumbhaar based their hypothesis upon the fact that not in all cases of agranulocytic angina is the bone marrow aplastic for granulopoietic elements--in fact it may even be hyperplastic. They pointed out that the general leukopenia of this disease involves not only the granulocytes proper but usually the lymphocytes and monocytes as well. Other elements are rarely affected. To them it seemed very probable that a maturation factor was at work, either arresting development of white cells in their formative centers or producing degenerative changes in them before sufficient development for normal migration into the blood stream, or possibly a combination of both factors. And finally they called attention to the analogy between agranulocytic angina and pernicious anemia. Pernicious anemia too has remissions and relapses; it too, is as yet an idiopathic disorder with probably a constitutional background of prime importance; it may be closely mimicked by other disorders; and its relapses are characterized by

ETIOLOGY

megaloblastic hyperplasia of the bone marrow caused, according to the modern view (Minot), by some maturation-inhibiting factor directed against the red cell series. This concept, transferred to the white cell disturbance of agranulocytic angina, would in no way deny the probability of a terminal, secondary destruction (or aplasia) of the bone marrow, spleen and lymph node cells in many instances, such as is known to occur in the bone marrow at the end (aplastic) stage of the untreated or poorly treated pernicious anemia case.

Miscellaneous: The theory of an abnormal destruction of neutrophils outside the bone marrow and the theory of storage of neutrophils in organs of the body are without sufficient proof for serious consideration and are practically eliminated by the findings at autopsy. Nutritional disturbances are advocated by a few but without evidence of any scientific research or proof.

MORBID ANATOMY

Epithelial Lesions: Epithelial lesions are present in practically 100% of all cases of primary agranulocytic angina as found at autopsy (30, 49 & 53) and are said to be merely a consequence of the absence of circulating granular leukocytes (2, 30 and many others) which under normal circumstances are so conspicuous in an inflammatory reaction, that is, with the loss of the normal physiologic barriers to the invasion of bacteria (neutrophils?), the bacteria upon the skin and mucous surfaces find easy ingress into the underlying tissues. The time of appearance of these lesions in relation to the time of onset of the subjective symptoms has been described as preceding, coincident with, or following the subjective symptoms. Probably these seeming conflicting observations are due to the degree of neutropenia and the virulence of the bacteria present. Generally speaking, with the development of oropharyngeal, vaginal or rectal lesions, pain is a coincident symptom.

These lesions are most often found in the oropharynx particularly in the region of the faucial tonsils, but are not infrequent in and about the anus, the vagina, the larynx, the urethra, and throughout the gastro-intestinal canal as a whole. Occasionally, necrotic lesions are found involving the skin. Oral lesions were present in 42 of the 43 cases reviewed by Rudner and Michelson (54) and in 15 of the 18 cases observed by Fitz-Hugh and Comroe (49). These findings are in keeping with the literature as a whole. Because of their marked

MORBID ANATOMY

frequency, recognition of the early stages of the oral lesion is of decided importance in making an early diagnosis and cannot be stressed too much since only by early diagnosis can directed treatment be instituted before complications make the case hopeless. Lesions found elsewhere are equally important but too frequently are not looked for in routine examinations; instead, they are more usually sought for only after the case is well advanced and diagnosis obviously apparent, or are found at autopsy.

The lesion of the oropharyngeal mucosa, as recently described by Costen (55), is, in its first stage, white with a yellowish cast, and with a tendency to undermine to a spot $\frac{1}{2}$ to 1 cm. away from the margin of the tonsils or gums. The mucosal change is always an ulcer or slough which follows a sudden undermining of normal mucosa with clinical and histological evidence of the lack of cell reaction or leukocytic accumulation for defense. This process is evident to the examining eye at the very beginning. It may be seen as a mottled yellowish spot in the center of the anterior pillar before the surface of the mucosa has broken down. It is also seen as a lemon-yellow dot $\frac{1}{2}$ cm. from the gum margin, when the lesion has begun as an ulcerative gingivitis. The necrotic tissue is always white or gray, but this pastel shade of yellow is imparted to the very early lesion by the white substance shining through what remains of pink or red mucosa.

In the advancing cases, the oral lesions are usually

MORBID ANATOMY

described as ulcerative with a dirty gray, yellowish white, greenish black, or grayish yellow membrane covering the lesion. Removal of the membrane leaves a bleeding hemorrhagic ulcer.

The late cases reveal dirty, sloughing, black or brownish gangrenous areas which have developed upon the site of the earlier lesions. These more advanced stages are the type of lesion most frequently described in the literature, probably because of the frequent delay in seeking medical attention and the very rapid development of necrosis.

The lesions found other than in the oropharynx differ in no particular way from these as just described. Incision made into any of the epithelial lesions does not reveal pus because of the absence of physiological leukocytic response to the bacterial tissue insult.

In 19 autopsies review by Rudner and Michelson (54), no granular cells were noted in the ulcerative lesions on microscopic examination. Sections through the ulcers usually showed an outer structureless layer of necrotic material covering cells in varying degrees of degeneration, sometimes with lymphocytic and plasma cell infiltration. Polymorphonuclear cells were strikingly absent and colonies of bacteria were strikingly present. The vessel walls were often necrotic and filled with hyaline and fibrin thrombi. Tice and Jaffe (53) have made similar observations and stress the following: in sections of the ulcerations of the mouth and vagina they observed not a single granulocyte; the necrotic tissue was usually exceedingly rich in micro-organisms and fused with the living tissue with-

MORBID ANATOMY

out a definite line of demarcation; and in the loosened connective tissue around the blood vessels there were accumulations of lymphocytes and of swollen histiocytes with a vacuolated cytoplasm--but no granulocytic elements. It is generally agreed that this lack of tissue reaction is due to the absence of the neutrophilic cell.

Smears from these lesions have revealed a great variety of organisms but no constant organism has ever been found.

Bone Marrow: The pathological findings in the bone marrow are very confusing and upon first consideration very disappointing. It is here that most observers have felt that an explanation of the underlying pathology might be found but sections of the bone marrow (both biopsy and at necropsy) have shown anything but consistent findings. The cases of agranulocytic angina in which the bone marrow reveals severe alterative changes or complete exhaustion of the granulopoietic tissue are in marked contrast to those cases in which the bone marrow is found to be normal or hyperplastic without apparent injury to the granulopoietic tissue.

Formerly it was considered that all cases of agranulocytic angina showed an aplasia of the granulocytic elements of the bone marrow with little or no change in the remaining myeloid elements. The latter observation still stands in large degree but not the former. Occasional instances of the hyperplastic bone marrow had been reported prior to 1932 (9, 47, 56 & 57) but these reports received little or no consideration until

MORBID ANATOMY

Fitz-Hugh and Krumbhaar (15) in 1932 reported three additional cases of their own in which they found a hyperplasia of granulopoietic tissue in patients dying with agranulocytic angina. Their observations and the subsequent observations of Fitz-Hugh (49) in conjunction with Comroe have been revolutionary in the newer concepts of the underlying pathology in agranulocytic angina and as a result, the following is presented from the original work of Fitz-Hugh and Krumbhaar:

"The current concept of the bone marrow changes in primary agranulocytic angina is that there exists, at least terminally, a more or less complete absence of white cells of the granular (myeloid) series. This granulocytic-aplasia concept has developed partly on the basis of bone marrow studies indicating an apparently selective disappearance of the granular leukocytes and their progenitors and partly on the basis of analogy to established findings in certain other conditions, such as benzol poisoning, with its selective attack on formative tissues of the granular cells and blood platelets.

"The possibility that such a concept may not be entirely well founded in fact, and may be misleading in implication, has come to mind from personal study of the bone marrow in three recent fatal cases. In one of these, the marrow of most of the bones examined contained active hemopoietic areas filled with myelocytes, promyelocytes, and myeloblasts, while the peripheral blood contained only 200 white blood cells per cubic millimeter (all lymphocytes). Similar, although less obvious,

MORBID ANATOMY

absence of myeloid white cell aplasia was found in the marrow of the other two cases. One of these died after months of illness characterized by repeated severe relapses and incomplete remissions. This patient's marrow in most of the bones was more nearly aplastic as regards granular series cells than any other marrow of such cases personally examined; but even this one showed numerous myeloblasts and a few myelocytes in the rib marrow, whereas her terminal white blood cell count was only 500 cells per cubic millimeter (all lymphocytes). Necropsy was performed in each case within two hours of death and fresh bone marrow smears were stained at once."

The following year (1933), Fitz-Hugh (49) in conjunction with Comroe reported the significant data of 18 cases of primary agranulocytic angina with 9 necropsies. The bone marrow findings showed a hyperplastic granulopoietic tissue in 7 cases, a normal or hyperplastic erythropoietic tissue in all cases, and no aplasia in any of the cases. Of note was the fact that polymorphonuclear cells were strikingly absent in each instance and there seemed to be an arrest of maturation beyond the myelocyte stage. This observation is the basis of the maturation-arrest hypothesis of etiology as proposed by Fitz-Hugh and Krumbhaar.

Although not commented upon by Fitz-Hugh, an analysis of the bone marrow findings in these 9 autopsies shows that whereas one bone may be degenerative for granulocytes, other

MORBID ANATOMY

bones in the body are frequently hyperplastic for these elements. This difference in the myeloid tissue as found in different parts of the body may account for the reports of aplasia of the granulocytic tissue by some men, particularly when only the bone marrow of the femur is examined as is so often the case. There is also to be considered the point of false interpretation of the status of gelatinous bone marrow. In our discussion of the physiology of myeloid tissue, it will be recalled that Sabin (17) said that gelatinous marrow has been repeatedly reported by pathologists as being degenerative or aplastic when in reality it is a true proliferative and regenerative process of the myeloid tissue.

In the Archives of Pathology (Nov. '33), Jaffe (30) gave a very comprehensive review of the bone marrow findings in agranulocytic angina to date and presented detailed histologic studies of the changes in the bone marrow in a series of 9 cases of his own. Five of the cases were idiopathic, two cases seemed to have developed during anti-syphilitic treatment, while the remaining two proved to be cases of prolonged streptococcus viridans septicemia. At autopsy there were found no essential differences in the bone marrow irrespective of the type, that is, whether primary or secondary. In four cases he found the bone marrow of the femur to be far more cellular than normal and in this hyperplasia the granulopoietic tissue took an active part.

MORBID ANATOMY

In the remaining five cases the cell content of the bone marrow of the femur was not increased and the destruction of the granulopoietic tissue did not follow an initial hyperplasia. In both the hyperplastic and the nonhyperplastic bone marrow, the granulopoietic cells revealed severe regressive changes which began in the specific granulations of these cells. This degenerative process continued until it caused the death of these cells. However, the myeloblasts, when present, were intact and, as pointed out by him, suggests that therapeutic attempts are not absolutely hopeless even in the acute forms of the disease. The erythropoietic tissue was not particularly altered. In the more prolonged cases, a moderate anemia developed but was not remarkable after consideration of the toxic state of such patients.

Miscellaneous: An analysis of the pathologic findings found at autopsy by practically all observers shows that other organs do not reveal any unusual or unique histologic changes and may be said to be secondary and essentially those of a bacteremia without polymorphonuclear response. The regional lymph nodes are frequently enlarged and it is not unusual to find some enlargement and hyperplasia in all the lymph nodes, particularly the mesenteric glands. The spleen and liver are moderately enlarged in about 50% of the cases and is said to depend upon the predominance of toxic or septic symptoms (2). There is frequently a generalized

MORBID ANATOMY

hyperplasia of the entire reticulo-endothelial system (2, 30 & 54). Congestion with red blood corpuscles is a usual finding in both the liver and spleen. The spleen shows a mobilization of the histiocytes while the Kupffer cells of the liver are not infrequently swollen and prominent and often mobilized (30). Areas of necrosis similar to the epithelial lesions are often found scattered throughout the internal organs. A very characteristic and constant finding throughout the body as a whole exclusive of the bone marrow is the absence of any oxydase positive cells (30 & 49). The kidneys show the usual findings as encountered in toxic degenerative processes.

Complications: The complications are invariably those associated with or secondary to sepsis. Their appearance closely parallels the developing toxemia in the patient. The most frequent complications encountered are: broncho-pneumonia, myocardial degeneration, bacteremia, pulmonary infarction, and toxic degeneration of the kidneys (2, 30, 49).

CLASSIFICATION

In a comprehensive study of those disorders characterized by an absence or near absence of granular cells in the peripheral blood stream, two major types are at once apparent. In one the etiology is unknown and the blood picture is primary: in the other, the etiology is known and the blood picture is secondary. A discussion of secondary agranulocytic angina is beyond the scope of this thesis and it is mentioned here only for clarification of the broad subject of the neutropenic state and to show the distinction between the primary and secondary types of agranulocytic angina.

The following classification, with slight amplification, is adapted from a recent review of this subject by Sachs (58). It is obvious that this is a clinical classification in the case of primary agranulocytic angina and an etiological classification in the secondary type.

A. Primary Agranulocytic Angina--Etiology unknown

- (a.) Acute - Schultz type: fulminating: mortality varying from 90 to 100%
- (b.) Recurrent - acute attacks separated by weeks or months, the blood picture during the interim showing a normal picture or a chronic neutropenic state.
- (c.) Chronic - may be physiologic for the individual or may be a manifestation of broken compensation of the granulopoietic organ: potentialities of an acute attack.

B. Secondary Agranulocytic Angina--Etiology known

- (a.) General Infection - influenza, typhoid fever, dengue, kala azar, small pox to fourth day, undulant fever, malaria, measles, extreme sepsis.

CLASSIFICATION

- (b.) Focal Infection - teeth, sinuses, tonsils, osteomyelitis, etc.
- (c.) Chemicals - arsenic, arsenical preparations, benzene, chemicals and drugs containing the benzene ring, lead, mercury, alcohol, ether, morphine: most of these act through chronic intoxication: some may be acute.
- (d.) Irradiation - X-ray, radium
- (e.) Blood Diseases - exhaustion of the marrow as seen in pernicious anemia, in rare cases of acute leukemia, and in the terminal stage of chronic leukemia: splenic diseases: aplastic anemia: some secondary anemias: aleukemic leukemia: malignant invasion of bone marrow.
- (f.) Malnutrition - cachectic or debilitated states

MANIFESTATIONS and COURSE

Types: The clinical types seen are variable and are probably a reflection of the degree of injury to or dysfunction of the granulopoietic tissue. The acute type is fulminating, with sudden onset, and with symptoms of a high degree toxemia. The blood shows a marked leukopenia and a total or near absence of neutrophils. The prognosis is extremely grave. The recurrent type is characterized by acute attacks several weeks or months apart. The patient is usually symptom free between attacks but often dies during a subsequent acute attack. The chronic type holds its chief importance in that the patient is in potential danger of an acute attack at any time.

Onset: After careful analysis, Roberts and Kracke (35) came to the conclusion that there are three onsets; a marrow onset, a blood stream onset, and a clinical onset, each occurring in the order named. They point out that there is little if any evidence that the granulocytes are formed normally in the marrow and destroyed abnormally in the blood stream. On the contrary, there is much evidence that the myelocytic function of the marrow slows down or stops (decompensates) and that the primary pathologic condition is in the bone marrow itself. They are convinced from experimental studies of their own and of Weiskotten (59) that the life of the granulocyte under normal conditions of health is not over five days. Consequently, should the granulopoietic organ stop functioning for an equal period of time, all granulocytes after this

MANIFESTATION and COURSE

lapse of time totally disappear from the blood stream, and it is not surprising that the most desperate symptoms should arise from (a) the loss of the powerful, normal, active immunity of the tissues conferred in large measure by the neutrophils and (b) the easy infection that results.

Similar views regarding the sequence of onsets, that is, marrow, then blood stream, and finally clinical, have been expressed by numerous other observers, notably Pepper (41), Doan (19), and Jackson et al. (60) and they submit conclusive evidence for their judgments.

With these three onsets in mind, a study of the symptomatology is greatly simplified and eliminates for the most part a separate consideration of the three types of primary agranulocytic angina because the clinical manifestations are largely directly proportional to the degree of neutropenia found in the peripheral blood stream.

Symptomatology--Marrow Onset: From a study of the blood stream onset, it is presumable that the marrow onset may be acute, recurrent, or chronic but in so far as can be found, it has never been observed. Apparently, there are no subjective symptoms nor any obvious objective symptoms at this time.

Symptomatology--Blood Stream Onset: The blood stream onset may be acute, recurrent, or chronic. In the few cases in which this onset has been observed, the observation has come more frequently by accident than design. From a review

MANIFESTATION and COURSE

of the literature it seems to be the popular belief that the acute blood stream onset is characterized by subjective symptoms of malaise, headache, weakness, fatigue, and a feeling of apprehension. The observations of Fitz-Hugh and Comroe (49) do not confirm this opinion. They state that they have seen patients with this disease (as well as patients with leukemia and other diseases) whose total granulocytes have varied from zero to supernormal numbers without any other symptomatic or objective change of status. Jackson et al. (60) likewise report that the leukopenia as seen in acute primary agranulocytic angina precedes any symptoms by several days and cite an instance in a patient known to have recurrent attacks and on whom routine white cell counts were made every day. In this case the white blood cell count was for three successive days at an approximate level of 500 cells per cubic millimeter and yet the patient felt perfectly well and was at her work. Only on the evening of the third day of leukopenia did the temperature suddenly rise to 104° F. and sore throat develop. From this case and from former similar observations, they conclude that in the acute type, the blood changes precede and condition the striking anginal symptoms.

An excellent clinical study of the chronic neutropenic state has been presented by Doan (19). In those individuals presenting the more chronic condition, he found that their symptoms were vague and very few signs other than the leuko-

MANIFESTATION and COURSE

penia itself were present. Taking the group as a whole he found that he was able to make further differentiation. In some, a count regularly totaling between 2,500 and 5,000 leucocytes per cubic millimeter did not seem to be incompatible with perfect health, and whenever any intercurrent pyogenic infection intervened, a leukocytosis promptly developed and no inadequacy in the response was apparent. Both quantitative and qualitative relationships within the white cells were normal, and the rhythm of delivery was normal. This group he concluded were individuals in whom a perfectly satisfactory and efficient cellular equilibrium was established, normal in every respect except that it operated at a level somewhat below that found in the majority of normal adults.

In the second group of patients who showed a chronic leukopenia of approximately similar grade, he found that there were apt to be somewhat less of the normal feeling of well being, some loss of energy, weakness, increased fatigability, a relative lymphocytosis, and an absolute neutropenia with a mild "shift to the left" but with no myelocytes present. In these patients any demand over and above that represented by the physiologic needs of the healthy body resulted in a more severe leukopenia rather than a compensatory leukocytosis. Very similar observations have been reported by Roberts and Kracke (35) and Mettler and Olsan (50) and have already been alluded to in the discussion of predisposing etiologic factors.

In brief summary it can be said that during the blood

MANIFESTATION and COURSE

stream onset, the blood picture is the only positive finding in the acute onset, and that a neutropenic state of varying degree, usually accompanied by symptoms of weakness and easy fatigue, are the only findings in the chronic onset.

Symptomatology--Clinical Onset: Indirectly the clinical onset of the chronic case has already been dispensed with in our considerations of the blood stream onset. The clinical onset of the recurrent type differs in no particular from the typical acute attack so that in the discussion to follow we shall be concerned only with the latter.

The clinical onset of the acute attack is usually sudden and dramatic. In a series of 18 such cases, Fitz-Hugh and Comroe found the symptoms of clinical onset to be: weakness and fatigue, 100%; malaise and feverishness, 100%; sore throat, 79%; sore mouth, 47%; cough, 34%; chills, 34%; vomiting, 26%; rectal distress, 18%; dysphagia, 10%.

Just what role the absence or near absence of neutrophils plays in the direct modification of these symptoms is not known, but without exception, these clinical manifestations may be interpreted as those of sepsis and toxemia.

Clinical History: According to Pepper(41), no age is immune; the records include patients from two weeks to sixty-six years of age. No seasonal incidence has appeared, nor has any geographic influence been observed. The condition is apparently not contagious nor familial. In a survey of 82 cases, Ordway and Gordon (61) found that the disease showed

MANIFESTATION and COURSE

a decided tendency to affect the female sex, at least 75% of the cases occurring in women. They also found that usually there was no history of ill health immediately antedating its beginning, although it may develop during a chronic illness. The mode of onset was nearly always acute, although prodromal symptoms of general malaise occasionally preceded its inception. The initial symptoms were high fever, 101°-105° F., sore throat, general malaise and difficulty in swallowing. Jaundice occurred in at least half of the cases. Chills, headache, vomiting, and general muscle pains frequently occurred. Bleeding from the mucous membranes was rare.

Physical Examination: The findings on physical examination, as set forth below, have been taken from a critical review of primary agranulocytic angina by Ordway and Gordon (61) who based their conclusions upon the details of 82 well described cases.

They found that the patient usually looked severely ill in all acute attacks. During the first few days, however, some cases failed to betray by their general appearance the nearly hopeless prognosis which awaited ahead. In the great majority of cases there was no pallor of the skin nor of the mucous membranes. A sense of exhaustion was common. The sensorium was particularly clear as a rule until just before death when coma many times supervened.

In the oral cavity, inflammatory changes of varying degree accompanied practically all cases. Of these, ulceration

MANIFESTATION and COURSE

and necrosis with membrane formation were by far the most frequent. The tonsils, gums, pharynx, tongue, larynx, or esophagus were the usual sites of the necrotic process. Lesions here were accompanied with severe pain. Ulcers in other portions of the gastro-intestinal tract, in the skin, and in the vagina often accompanied the oral lesions. Wherever their location, the ulcers had a similar appearance due to a peculiar lack of cellular response. The membranes were most often described as non-marginated with overhanging edges or with no surrounding inflammatory reaction. Microscopic examination showed little cellular reaction and as a rule, complete absence of polymorphonuclear leukocytes.

Petechial hemorrhages of the skin and spontaneous hemorrhages into the viscera occurred occasionally but were not the rule. Such hemorrhagic tendency appeared to be independent of the number of platelets which were usually normal. Jaundice of moderate degree was found in 50% of the cases.

Enlargement of the lymph nodes draining the oral cavity occurred in about one-half the cases. Other regional lymph nodes were involved in about the same ratio according to the location of the ulcerations. Generalized lymph gland involvement was rare.

The liver and spleen were enlarged in about one-half the cases and then only of moderate degree.

Laboratory: Cultures made from the ulcerations yield a great variety of organisms with no one type predominating.

MANIFESTATION and COURSE

Positive blood cultures (present in 50 to 60% of all cases according to various observers) show the same results.

The white blood cells are always markedly reduced in number in the peripheral blood stream. Ordway and Gordon (61) found the average leukocyte count in 82 cases was 1,210 per cubic millimeter while the lowest count was 100 per cubic millimeter. They also found a progressive decrease in the number of white blood cells usually accompanied the course of the disease. The polymorphonuclear leukocytes sank to minute percentages (av. 4%) or vanished entirely from the blood smear. Young granular cells were strikingly absent. The resulting relative lymphocytosis varied from 60 to 100% while their absolute number was normal or reduced. Monocytes were reported as ranging from 0 to 18%. In some cases abnormal lymphocytes were noted. In the series of 82 cases reviewed, the erythrocytes were present in normal numbers in 49 instances, 11 cases showed a moderate secondary anemia, and in 22 cases there was no record of a red blood cell count. Blood platelets were usually normal in number.

Clinical Course: The course of this disease in the acute attack is astonishingly rapid. The complications, as already described under "Morbidity Anatomy", set in with the onset of the clinical manifestations or follow within a day or two thereafter. Ordway and Gordon found the average duration of the disease in the acute type was from 4 to 10 days, the shortest 2 days, and the longest 90 days. Thus it is seen that not a moment can be spared before a rational treatment is instituted.

DIAGNOSIS

The outstanding diagnostic feature in primary agranulocytic angina in the acute type is the blood picture. It was upon this basis alone that Schultz (1) originally separated this disease from other blood dyscrasias and today it still remains our only means of making a positive diagnosis. Kastlin (10) has very adequately summarized the blood picture as follows:

"The blood changes are highly characteristic. The red cells, hemoglobin, and platelets are normal or at most but slightly diminished. There is a rapidly progressive diminution in the number of granular leukocytes which may totally disappear. There are usually no myelocytes or myeloblasts. The absolute number of lymphocytes is also reduced, so that the total leukocyte count falls usually below 2,000 and may be as low as 100 per cubic millimeter of blood."

Subsequent observations have confirmed these criteria and in addition have shown that the blood picture is diagnostic even before the onset of any subjective or objective symptoms (19, 41, 49 & 60).

The blood picture in the chronic and recurrent types has already been described under "Manifestations and Course."

DIFFERENTIAL DIAGNOSIS

Secondary Agranulocytic Angina: Many of the secondary types of agranulocytic angina are repeatedly confused with the primary type, notably acute or insidious poisoning and those due to sepsis. The possibility of chemical or toxic agents is best ruled out by a very careful history of the case and an appreciation of all those factors known to cause the secondary type of disease. These factors have already been enumerated in our classification. Generally speaking, the blood picture in the secondary type is not typical even though a marked leukopenia exists--secondary anemia is frequently a prominent finding and usually there is not a selective abnormality reserved to the granulocytes.

Occasionally, cases of septicemia show a gangrenous stomatitis and a clinical picture and course identical with primary agranulocytic angina. Schultz (1) insisted, however, that they belonged to another group and pointed out that in such instances there is always a positive blood culture, a well defined hemorrhagic diathesis, a decrease in blood platelets, an outspoken anemia, and a septic type of spleen at autopsy.

Aplastic Anemia: Ordway and Gordon (61) have stated that the classical symptoms in aplastic anemia are a sub-acute course, tendency to affect young persons, striking pallor, hemorrhages into the skin, bleeding from mucous membranes, and ulcerative lesions in the larynx. No or slight enlargement of the lymph glands is present: the

DIFFERENTIAL DIAGNOSIS

liver and spleen are not enlarged. Blood examination shows a marked reduction of the erythrocytes and blood platelets, a low total leukocyte count, and a relative lymphocytosis. In agranulocytic angina the onset and course are much more acute; no pallor is present; there is but rarely a hemorrhagic diathesis; and the erythrocytes and blood platelets are never more than moderately reduced, their number generally being normal. The above differential diagnosis is essentially that of Schilling (13) also.

Infectious Mononucleosis: This disease, while resembling agranulocytic angina in the ulcerative throat lesions and relative lymphocytosis, is much more benign. A definite leukocytosis is present at some stage of the disease and white cell counts of a few hundred cells with almost total absence of the polymorphonuclear cells are not encountered (61).

Diphtheria: A large number of the cases of agranulocytic angina when first seen have been diagnosed as diphtheria because of the membranous throat lesions. The absence of diphtheria bacilli in the throat culture and the severe leukopenia should adequately serve to differentiate the two diseases.

Aleukemic Leukemia: According to Lucas and Washburn (62) the patients in this group may have either the lymphatic or myelogenous form of the disease without any marked increase in the leukocytic count although the rest of the clinical picture as well as the findings at autopsy may be identical with those of a typical case of leukemia. These cases may

DIFFERENTIAL DIAGNOSIS

show almost any white blood cell count from 500 to 10,000. The blood smears will always show some of the immature cells which are characteristic of the leukocytic hyperplasia. Some never show a leukocyte count above normal although followed for months, while others have shown a leukopenia either preceding the typical leukocytosis or as a terminal event. Reduction of the erythrocyte count, hemoglobin, and platelet count may be expected to parallel those described in the other leukemias.

As pointed out by Ordway and Gordon, there are many clinical manifestations which are similar in both aleukemic leukemia and primary agranulocytic angina, such as acute onset, high fever, prostration, ulcerative processes on the mucous membranes, regional lymph gland enlargement, and slight or no enlargement of the spleen and other lymph nodes. However, they state that aleukemic leukemia differs in that the leucocyte count as a rule increases during the course of the disease to 30,000 or more, is practically always accompanied by a hemorrhagic diathesis, there is invariably a rapid fall in the erythrocyte count and hemoglobin, and there is always a high percentage of abnormal primitive cells, either myeloblasts or lymphoblasts, in the blood smear. Much the same differential points were used by Schultz (1) and Schilling (13).

Rosenthal (14) found that after a small injection of adrenalin (1.0 mgm.) a marked rise of leukocytes in the peripheral blood stream occurred in normal individuals and in

DIFFERENTIAL DIAGNOSIS

patients with aleukemic leukemia and aplastic anemia. In several cases of primary agranulocytic angina, adrenalin injection produced only a slight increase in the leukocyte count. He suggests that the adrenalin reaction may prove to be an important diagnostic aid in differentiating the genuine cases of agranulocytic angina from allied conditions.

PROGNOSIS

A true estimate of the mortality in primary agranulocytic angina is made difficult by the failure of sharp differentiation between primary and secondary types by many observers, and there are probably many cases which recover but which are never diagnosed. In the original six cases reported by Schultz (1), the mortality was 100%. Five years later, 1927, Kastlin (10) was able to find only 43 cases in the literature but with a mortality of 95%. In 1931, Harkins (63) reviewed the literature and in a series of 150 cases, reported a mortality of 82%. This apparent reduction in the mortality rate is probably due to the recognition of more cases owing to more critical studies of the blood and thereby the inclusion of the more chronic cases in the group.

More recently, with so-called specific therapy, Jackson et al. (60) have reported 54 cases of the primary type treated with nucleotide K96 with a mortality of only 30%; Reznikoff (64), a series of 15 cases treated with adenine sulfate with a mortality of but 27%. Figures given by Doan (19) in 1932 for cases treated with blood transfusions alone are, 54 cases, mortality 64%; treated with irradiation alone, 64 cases, mortality 53%. In 1933, Fitz-Hugh and Comroe (49) reported 18 cases treated with miscellaneous agents with a mortality of 78%. A similar series of 38 cases treated likewise with miscellaneous agents is reported by Delatour (48) with a mortality of 58%.

PROGNOSIS

Briefly it may be said that chronic and recurrent types have the potentialities of becoming an acute type and in the acute type the prognosis at best is extremely grave and is dependent upon the resumption of granulopoietic function--the prognosis being still poorer if this return of function is preceded by the onset of complications.

THE RATIONALE of TREATMENT

A review of the literature shows that most authors believe that no satisfactory, much less a specific treatment, has as yet been discovered for primary agranulocytic angina. Many things have been tried but their effect upon the course of the disease is not well established. When the cause is discovered, the cure may be more intelligently sought and more easily found.

Although certain groups report excellent results with a certain type of therapy and enthusiastically recommend its use above all others, when this same treatment is applied by the physician at large, the results as a whole are usually very disappointing. These latter results perhaps carry hidden fallacies--too often before a diagnosis is made the case is hopelessly beyond control with complications that would almost certainly be fatal even with an intact bone marrow, and, too often in a frantic search for a so-called specific treatment, the already very sick patient is subjected to a whole host of procedures, some good but some of questionable or even of harmful value. Almost axiomatically it may be stated that the longer a case lives the more types of treatment he has had. Too, there are those occasional cases which recover spontaneously after the most alarming symptoms and with no treatment whatsoever or even with a contraindicated type of therapy (see arsphenamine to follow).

So, to attempt an evaluation of the numerous treatments advocated in the acute attack becomes very difficult to make

THE RATIONALE of TREATMENT

because of so many conflicting reports by the various investigators, the lack of satisfactorily controlled therapeutics, and the too hasty expression of opinions in the literature condemning or condoning a particular type of therapy, such opinions being based upon very inadequate grounds.

Going back to the introductory remarks in our considerations of the physiology of myeloid tissue, it was stated that sound principles of treatment are invariably based upon an understanding of normal physiology and an appreciation of pathological physiology, both of which have been discussed. In our considerations of morbid anatomy we found that there were three outstanding findings;--the ulcerations of the mucous surfaces, a decompensating bone marrow, and a rapid onset of grave complications directly attributable to sepsis and toxemia. With these points in mind, the rationale of treatment, directed particularly to the acute attack, becomes:

- (a.) Prophylaxis
- (b.) Early diagnosis
- (c.) Elimination of all drugs or other agents known to cause secondary agranulocytic angina
- (d.) Care of local lesions
- (e.) Supportive treatment
- (f.) Anticipation of complications
- (g.) Use of "specific" treatment

Prophylaxis: The statistical studies on chronic leukopenic states made by Roberts and Kracke (35), Mettler and Olsan (50), and Doan (19), all of which have been reviewed,

THE RATIONALE of TREATMENT

are significant of the existence and potencialities of a hypofunctioning granulopoietic organ but there is little definite information available as to the management of chronic cases or of the prevention of recurrences. Roberts and Kracke have reported restoration of granulocytic function in a number of chronic cases with rest in bed alone. They also advise freedom from mental or emotional strain. Doan (18) experimenting with pigeons by underfeeding, reduced the red bone marrow to an extreme hypoplasia in just a short time. This indicates the necessity of an adequate diet. Beck (2) has had good results in the recurring type by feeding a high vitamin B diet with local treatment of the mouth alone. Thinking back to the theories of etiology and the causes of the secondary types of agranulocytic angina, in addition to rest in bed and an adequate balanced diet rich in vitamins, a rational program of prophylaxis in these individuals would include an elimination of all agents and particularly drugs known to have been implicated in precipitating attacks of agranulocytic angina in the past, an eradication of all foci of infection, scrupulous hygiene, and a careful watch kept of the blood picture.

Early Diagnosis: The importance of early diagnosis cannot be stressed too thoroughly because of the fulminating course of this disease and the rapid onset of severe complications. Routine blood counts and blood smears on all patients should be made and studied with great care. Those having a granulo-

THE RATIONALE of TREATMENT

penia should be under very watchful observation and checked by frequent analysis of their blood pictures.

Elimination of All Drugs or Other Agents Known to Cause Secondary Agranulocytic Angina: This measure applies to the acute case even more strongly than to the chronic or recurrent cases mentioned above. Too often, symptomatic treatment for the relief of pain in the past has embraced the use of drugs containing the benzene ring.

Care of Local Lesions: Undoubtedly the local lesions require attention but it matters not so much what measures are used so long as sloughs are cleared away and the parts cleansed at frequent intervals. Certainly no antiseptic that will cause a chemical destruction of tissue should be used. Delatour (48) recommends hot saline irrigations every three hours followed by local applications of hydrogen peroxide and sodium perborate. Others prefer a local application of saturated potassium chlorate solution. Costen (55) stresses the value of ultraviolet light.

No incisions should be made, wherever the lesion, because no abscess forms during the existing granulopenic state and incision but carries the infection deeper. Many pathological conditions clear themselves very rapidly as soon as the granulocytes return to the blood stream.

Because of the absence of tissue reaction, no surgery should ever be attempted in the acute phase. The most strict asepsis must be maintained in venipuncture or biopsy because

THE RATIONALE of TREATMENT

sepsis and sloughs are frequent followers of such procedures. Many men refuse to do biopsies of the bone marrow because of this great danger alone.

Supportive Treatment: This phase of treatment is concerned not only with the immediate state of the patient but should anticipate complications. The first step is to exercise complete control of the patient and maintain absolute rest in bed. Dysphagia is often a very serious problem. The forcing of an adequate diet in an extremely ill patient is probably inadvisable. However, intravenous glucose-saline solution should be started early and continued to the end because the therapeutic value of glucose and water in combating toxemias is on a very well established basis (Gager and Speer, 65). Digitalis has the same use as in any other toxemia. Hyper-ventilation of the lungs by means of carbon dioxide inhalations two or three times a day may forestall the development of broncho-pneumonia.

Although blood transfusions are frequently employed as the sole therapeutic measure in many cases, their use is certainly that of supportive treatment rather than as an agent directed at the underlying pathology. Their rationale is a subject of much speculation and debate. It is an established fact that repeated transfusions lower the rate of erythropoiesis (17). By analogy, many believe that transfusions lower the rate of granulopoiesis but no experimental nor clinical work has shown that transfusions either lower or increase the granulo-

THE RATIONALE of TREATMENT

poietic rate (2). On the other hand there are those who have successfully treated a considerable number of cases with transfusions and who feel that transfusions are of deciding value in many instances (31, 40, 41, 48, 55, 58, 66 & 67). Writing in the Medical Clinics of North America, 1932, Griffith (67) strongly endorses small daily transfusions. Delatour (48) and Hartwich (66) urge the same type of treatment and state that the transfusions should be started at the earliest possible moment. Mazet and Daumas (40) advocate their use and have had good results with this therapy alone but point out that as the case progresses it often becomes impossible to match a donar's blood with that of the patient. In the estimation of Sachs (58), blood transfusions are valuable, their only contraindication being a severe reaction following transfusion. This contraindication probably is an expression of the same thought as that of Mazet and Daumas. In all, the balance of clinical evidence is in favor of this type of supportive treatment and, exclusive of reactions following transfusion, the contradictions appear to be more imaginary than real. It would seem that their rationale is splendidly expressed by Pepper (41) who states that repeated transfusions should be employed daily to tide over the interval until the patient's bone marrow is given a chance to resume its function again.

"Specific" Therapy--Miscellaneous: Since the original description of this disease in 1922, innumerable agents have

THE RATIONALE of TREATMENT

been tried with a hope that a specific therapy might be found. These have included blood serum, streptococcus antitoxin, diphtheria antitoxin, leukocyte extract, bone marrow extract, whole blood subcutaneously, fetal liver, omnadin, and a great variety of foreign proteins--all of which were given with the hope that stimulation of the bone marrow to delivery of granulocytes would result, but all of which have shown no therapeutic results. For the most part they have but served to demonstrate that there is something more fundamentally wrong than the lack of a stimulus to call granulocytes into the blood stream. Intravenous injections of gentian violet, mercurochrome, and acriflavine have been used,--probably for the blood stream infection for they will not stimulate the production of granulocytes.

"Specific" Therapy--Arsphenamine: Because of the ulcerations found so often in the throat and the not infrequent isolation of Vincent's spirochaete from these ulcerations, arsphenamine or similar arsenical preparations have repeatedly been recommended for local application to these lesions (32 & 41). And, carrying this mistaken idea of etiology still further, there are those who use and recommend intensive arsphenamine therapy intravenously or in the transfused blood (32 & 68)! Too many cases of agranulocytic angina have been precipitated (primary or secondary?) by the use of arsenical preparations for this type of treatment to even be considered except from the negative view point.

THE RATIONALE of TREATMENT

"Specific" Therapy--Liver Extract: Since liver extracts have been shown quite conclusively to contain a maturation factor for erythrocytes in pernicious anemia (21 & 22), they have been administered to patients with agranulocytic angina with the hope that they might contain a maturation factor for granulocytes as well. In our consideration of the maturation and chemotactic factors in the physiology of myeloid tissue, it will be recalled that no clinical nor experimental evidence showed that the use of present day liver fractions produced a maturative effect upon the granulopoietic tissue. Perhaps with a different liver fraction, different results will follow but with the present day fractions the rationale of this type of treatment is without foundation.

"Specific" Therapy--Irradiation: This type of treatment, first suggested by Friedemann (59) has shown fair therapeutic value in the hands of certain investigators, notably Friedemann, Waters and Firor (70), and Gager and Speer (65). There are many others who have used identical technique who report negative results (2, 41, 55 & 66) so that clinical evidence allows no conclusions. Its rationale is open to question because there is no evidence that a cell per se is affected by the roentgen ray other than in a destructive manner. However, the exact mechanism of its action in this disease is uncertain, that is, whether a direct effect is exerted upon the bone marrow or an indirect effect takes place

THE RATIONALE of TREATMENT

due to irradiation of other tissues. Doan (19) has stated that its sole value is in cases with a hyperplastic bone marrow--by a destruction of intact myeloid foci, an autogenous nucleotide is liberated which then initiates the maturation and delivery of granulocytes from the remaining myeloid foci. Next to nucleotide therapy itself, cases treated with irradiation show a lower mortality rate than cases treated with any other measure so that further investigation may prove valuable. As this form of therapy stands today, it may precipitate a complete aplasia and fatal termination in those cases having a hypoplastic bone marrow..

"Specific" Therapy--Nucleotides: The use of nucleotides or their degradation products, adenine and guanine, in the treatment of agranulocytic angina has shown by clinical investigation to be the one outstanding therapeutic agent in this disease (see Prognosis). In addition, this type of therapy in the light of experimentation on laboratory animals seems to have a firm foundation. The years of research that lead up to the clinical application of these products has already been considered in our studies of the physiology of myeloid tissue. Although many physicians have reported negative results with this therapy, the clinical work of Jackson et al. (60), Reznikoff (64), and Doan (19) deserves much consideration. Their number of cases treated (primary types) now total 76 with only a mortality of 25 to 30%. This same

THE RATIONALE of TREATMENT

treatment has been used by them with equally good results in the secondary types of this disease.

It is of interest to note that whereas the maximum granulocytic response occurs on the fifth to sixth day following the injection of pentose nucleotide, the same response occurs in about 48 hours when adenine sulphate is used. This would suggest that the smaller molecule is more rapidly effective than the larger one, and if true, adenine sulphate would tend to better eliminate the development of complications. Too, injections of adenine sulphate are followed by very few reactions, while some type of reaction is not at all infrequent following the injection of pentose nucleotide.

SUMMARY

The present day aspects and status of primary agranulocytic angina have been presented. It is a grave disease characterized by marked leukopenia and a great reduction in the percentage of granulocytes. Its course may be chronic, recurrent, or acute. Although its original description was in 1922, more than 500 cases have been reported which intimates that its frequency is increasing. Whether it is a clinical entity or only a symptom complex is uncertain.

The etiology is still unknown but in the light of studies made, there is known to exist in many individuals a condition of hypofunction in the granulopoietic tissue. With evidence at hand, the acute attack suggests a sudden break in the compensation of the granulopoietic organ. Whether this break is due to an extrinsic or an intrinsic factor is uncertain but this factor apparently influences the maturation of the granulocytic elements.

The basic pathological findings are in the myeloid tissue which may show degeneration, a seemingly normal state, or hyperplasia. These findings are probably the manifestations of myeloid reaction to decompensation, the reaction being influenced by the degree of decompensation, the previous state of functional ability, the reserve strength of the tissue, the intensity of the noxious factor, the element of time, and the onset of complications. Other pathological findings are essentially those secondary to sepsis and toxemia.

Diagnosis is made by the blood picture alone, the out-

SUMMARY

standing characteristics being a marked leukopenia, an absence or near absence of granulocytes, no young forms, essentially normal lymphocytes and monocytes, and with little or no alteration in the erythrocytes and blood platelets.

The rationale of treatment is intimately concerned with prophylaxis, early diagnosis, elimination of all drugs or other agents known to cause secondary agranulocytic angina, the care of local lesions, supportive treatment, and the anticipation of complications. Laboratory and clinical evidence shows that of all the so-called specific treatments, nucleotide therapy is the only one that has shown any demonstrable results. Irradiation probably works through the medium of autogenous nucleotides.

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